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Before the Subcommittee on Oversight and Investigations, US House Committee on Energy and Commerce: "At What Cost: Oversight of How the IRA's Price Setting Scheme Means Fewer Cures for Patients." Sept 20, 2023

Chairwoman Rodgers, Chairman Griffith, Ranking Members Pallone and Castor, and members of the Subcommittee, I am Dr. Steve Potts, a biotechnology scientist and entrepreneur who has been working in the cancer field for the last 25 years to create new drugs and diagnostic tests. Thank you for the opportunity to testify today on the Inflation Reduction Act (IRA) and the impact that its nine-year penalty is already having on small molecule drug research and development.

I am here today to share two observations that I hope inform the committee's efforts to mitigate the unintended and negative impact of the IRA on new small molecule R&D, Medicare patients, and future patients, which is all of us.

1) The IRA has made new small molecule R&D for diseases of the aging nearly impossible – which is particularly bad not just for small company drug developers like me, but also for people who suffer from diseases like cancer and Alzheimer's. [1]
2) Congress can mitigate IRA's unintended and harmful impact on new small molecule R&D in a revenue neutral way. Were the government to begin price negotiations for both small and large molecules equally at 13 years it could, in exchange, increase the IRA's minimum statutory 35% discount to 42%. This change would then pay for itself: biotech

[1] https://rapport.bio/all-stories/post-launch-pre-cliff-rd-congress-ignores?rq=wong

> manufacturers themselves would bear the cost. That's how small a change it would take to preserve R&D.[2]

I am supportive of many aspects of the IRA, including the way it begins to address high patient out-of-pocket costs, as well as how it ensures that the prices society pays for biologic medicines comes down after an initial patent-protected period of market-based pricing, 13 years after their launch. That's long been the bargain: the drug industry makes medicines that are meant to go generic without undue delay and society makes them affordable to patients through proper insurance, which means low out-of-pocket costs. The best aspects of the IRA re-affirm this bargain.

IRA's impact on new small molecule R&D for diseases of aging

Unfortunately, the nine-year penalty harms new small molecule R&D by cutting deeply into the period of market-based incentives intended by the patent system. From 2019-2021, the FDA approved 177 new drugs. Fifty-one of those were in oncology and more than half of those (27) are small molecules. Less than 5% of cancer drug candidates that start first-in-human trials actually make it to market, and it often takes a decade of work to generate enough data to prove that a drug is safe and effective. It takes evidence from hundreds, sometimes thousands, of patients for a drug to be approved. Our industry spends a minimum of $200,000 per patient on direct clinical trial costs alone. Those fees go to academic medical centers and hospitals across America and the world. One successful drug in 30 years of post-PhD drug hunting is considered a productive career. Ask a room full of retirement-age drug developers to raise their hands if they've cured cancer in mice: Nearly everyone would raise their hands. But ask the follow-up:

[2] https://nopatientleftbehind.docsend.com/view/a3j6n93axkru3ckp

"*Raise your hand if you have a successful cancer drug approved for patients*?" Just a few hands would go up.

My own career is a good illustration. Since completing my PhD at University of California Davis in 1999, I've been involved cancer drug R&D for more than 20 years, first from a pathology angle and over the last decade in small molecule and biologics drug development. I've been on teams with two successful drugs that are currently given to patients. I'm one of the lucky ones.

At a small company called Ignyta, we successfully developed the drug entrectinib (now Roche/Genentech's www.rozlytrek.com). It is a well-tolerated daily pill with none of chemotherapy's side effects, with almost unheard-of response rates in difficult-to-treat, late-stage cancers. The drug acts on a specific mutation called TRK. TRK ignores the classical organ divisions – so whether the patient's cancer is in the lung, colon, breast, or thyroid, Rozlytrek can make an incredible impact. One patient that was in hospice with stage IV lung cancer had 15-20 brain metastases completely wiped out, and children with lethal brain tumors had remarkable responses. These are what molecular oncologists call "Lazarus patients." A few years ago at Barrow Neurological Institute in my home state of Arizona, a top brain cancer doctor pulled me aside in the hallway and raved about a patient that was on this drug that saw immediate tumor shrinkage -- "*Steve, I went to graduate school years ago in the hope that one day in my medical career I would see a response to therapy like we just saw in this brain cancer patient*." It is a highlight of my career. Drugs like this, the one in 20 that make it, keep all of my biotech industry colleagues motivated to press on developing better drugs against these horrible diseases. This drug wasn't a blockbuster in sales, but it is an example of how critical these drugs are for the patients they serve.

Drug development is a long-term process and the investors who fund portfolios of drug candidates need to project returns ten to fifteen years from now. Each project starts with an idea

and eventually we get some data from treating mice. That's table stakes. If you can't at least cure cancer in mice you aren't likely to get any real investment and get the biotech company off the ground. If this were the movie industry, this first drug idea is like having a draft of a script. A script idea for a professor with a whip and a fedora looking for treasure is a long, long way and hundreds of millions of dollars of investment from an actual blockbuster Indiana Jones movie playing on screens nationwide! Some of these ideas come from universities and government funded research, but the majority of the successful drug "movie script" cancer cures in mice come from within the biotech industry. But in all cases, the actual making of the movie is done by industry. And America dominates this global industry, from coast to coast. I am proud of my industry; it is a quintessential American enterprise. I hope you are proud too. Our industry is funded largely by investors. And I don't mean billionaires, though they play a role. I mean pension funds. It is regular Americans whose retirement savings, via professional investors, are being invested across the market, including into drug development. It's university and hospital endowments. Our 401k plans are invested in biomedical innovation. We should all be proud, but I think too few people know to be.

Professional investors ensure that only the best projects with the highest chances of good returns for their own investors get funding. Everyone likes to point to the failures and play Monday morning quarterback, making investors seem foolish for backing bad bets, but that's not what I experience. Investment analysts really put you through the ringer. They put everyone through that. They get quite a few things right. The results speak for themselves. Look at all our progress. Look at all the diseases we treat with medicines that would have landed people in hospitals decades ago.

I tell my family and friends that biotech fundraising is like "Shark Tank for nerds." I usually have just a few minutes to explain to a roomful of smart PhD and MD investors what our drug does, why I believe our data in mice will translate to a cure in people, and generally (hopefully)

convince investors that my team and I know what we are doing. I do this many times and expect to hear a lot of “no thanks.” At my last company, a cancer immunotherapy company, I had 100-plus “Shark Tank for nerds” meetings before I finally got the funds to start the company. To initially get the company going took 18 months of fundraising, working without salaries. We raised $25M and then a second round of $50M and worked to get close to a go-ahead from the FDA to be able to start first-in-human clinical trials. GMP manufacturing, toxicity testing, efficacy studies, regulatory work, patent protection, a continued favorable competitive window – all of this has to come together to just initiate the first-in-human studies. But after four years of work and building a team of 20 people, unfortunately we had a conclusive data package that showed that the drug wasn’t good enough. Even with $50M in the bank, we paused development. You don’t want to waste patients’ lives on clinical trials of drugs that aren’t good enough. We learned from our setback and now we are back to the drawing board with a new team and a new drug idea.

But the government gave CMS the power to set as low a price as it likes on what Medicare pays for small molecule drugs merely nine years after they launch, which cuts deeply into the period of market-based incentives intended by the patent system and halves these medicines’ value to investors and researchers. Those drugs have been going generic about 14 years after launch ever since the Hatch-Waxman Act of 1984 made it possible for small molecules to go generic. Since the way innovation works is that investors and companies fund portfolios of projects and generate a return only from the small fraction that succeed, cutting the value of the successes in half makes the whole portfolio of investments non-viable. Already, investors are turning away from small molecule development for diseases of aging that don't have some kind of exemption from the nine-year penalty. It’s made it much harder for my team to find funding for the cancer drugs we are working on. Now every investor asks “How are you going to develop your drugs in

a way that earns an exemption from the IRA?" I don't blame them for asking. I understand that nine years is too little time.

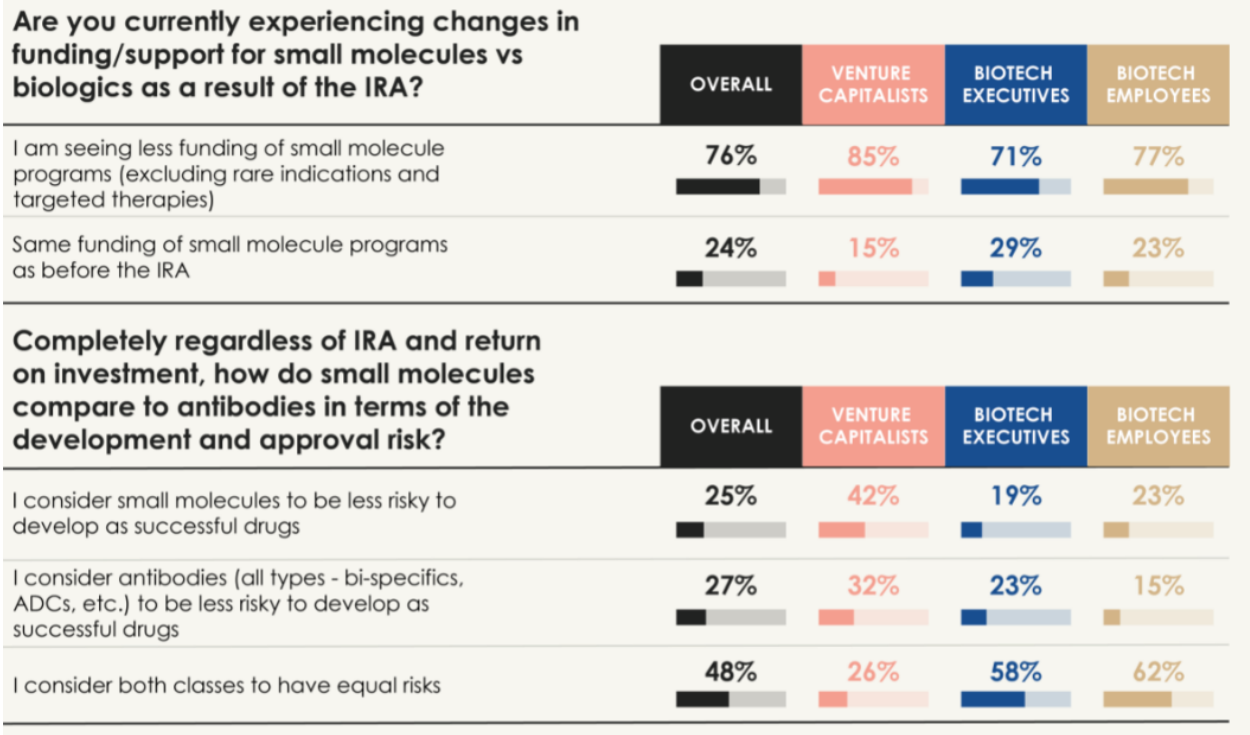
To my knowledge, there has never before been a policy that overrode the intent of the patent system with government price setting. It's not like the government is negotiating what it will pay ahead of R&D investment. That, at least, would be a precedented alternative to the framework we have now. For example, when the government wants to know in advance how much or how little it will spend on a new invention, it will enter into a forward-contract with a company. Only when the contract is signed will investors fund that project. Instead of the market, they have the contract to assure them that there will be an adequate reward if they succeed. But the IRA is not that. The IRA expects investors to risk their capital, fund the launch of the drug, and then, after investors have generated only part of the revenues that the patent-system and market would have allowed, the government steps in at nine years to dictate the rest. There has never been an example of investors funding R&D with that kind of incentive framework.

About a year ago while out fundraising I noticed a fundamental shift by investors away from small molecules, especially for drugs for diseases that are more common among older Americans. This was a real investment question I had during a pitch: "Is there any way you can change from your small molecule daily pill approach in these cancers to making it a more complex biologic injectable?" Imagine being in a boardroom with someone developing one of these remarkable novel cancer fighting daily pills for the first time, and being asked to try making it into a needle-delivered format or an IV hospital infusion instead of a pill? Entirely for economics! The IRA is encouraging companies like mine to pivot away from small molecules that have highly predictable patent cliffs and toward biologics that do not.

I was curious about this anecdotal experience in my own investor pitches – was I the only one seeing this? After the IRA had been in place for six months, I did my own survey. I surveyed

over 100 venture capitalists, biotech leaders, and drug development executives, asking two questions: 1) Has the IRA already impacted plans for small molecule investment and 2) Do you consider biologics or small molecules as more risky?

The damage was clear: six out of seven biotech investors were *already* pivoting away from small molecule drug development. Another study by BioCentury[3] reached the same conclusion.



Are you currently experiencing changes in funding/support for small molecules vs biologics as a result of the IRA?	OVERALL	VENTURE CAPITALISTS	BIOTECH EXECUTIVES	BIOTECH EMPLOYEES
I am seeing less funding of small molecule programs (excluding rare indications and targeted therapies)	76%	85%	71%	77%
Same funding of small molecule programs as before the IRA	24%	15%	29%	23%

Completely regardless of IRA and return on investment, how do small molecules compare to antibodies in terms of the development and approval risk?	OVERALL	VENTURE CAPITALISTS	BIOTECH EXECUTIVES	BIOTECH EMPLOYEES
I consider small molecules to be less risky to develop as successful drugs	25%	42%	19%	23%
I consider antibodies (all types - bi-specifics, ADCs, etc.) to be less risky to develop as successful drugs	27%	32%	23%	15%
I consider both classes to have equal risks	48%	26%	58%	62%

Figure 1. Author's survey of the damage of IRA small molecule penalty (over 100 investors and executives). Full report at https://www.nopatientleftbehind.org/publications/ira-impact-on-small-molecule-development

Do we really need to wait for the larger studies to read out, like a failed Phase 3 cancer study? The trend is already clear. The cancer of the IRA nine vs 13 small molecule penalty will continue to metastasize, eliminating previously promising drug programs in cancer, neuroscience, orphan diseases, and many other areas. I can't imagine that there is anyone in this room who deliberately designed IRA to have this kind of crushing effect on small molecule drug

[3] https://www.biocentury.com/article/647205/ira-survey-biotechs-bracing-for-impact

development, but this is the reality. I wish it didn't take as much money as it does to develop a new drug, but that is also a reality. Where does that money go? It largely funds American hospitals and clinical trial research centers, via clinical trials as well as hundreds of thousands of skilled American employees in your home state and mine. Investors in biotech have to get a return on their risk, and the elimination of four years between nine and 13 cuts their potential return in half. Any rational investor would leave the small molecule space faced with these alternatives, and they will leave the biologics space too if we mess further with the already shortened 13-year patent-like period of market-based pricing.

While the nine-year penalty's effects are being felt by small biotech companies like mine and impacting R&D decisions at large pharmaceutical companies, too, ultimately patients, which is to say all of us, will bear the burden. We can make a bipartisan fix to this small molecule penalty in a revenue neutral way, and we must come together to do this if we wish to continue to make progress in treating and curing cancers and other diseases of aging such as Alzheimer's that threaten us all and are largely covered by Medicare.

If one cares only about how much we spend on drugs, then not paying for drugs will make it seem like we are saving money. But consider the hundreds of billions of dollars that dementia costs us each year in hospital and nursing home costs. And as our population ages and we solve other diseases, allowing us to live longer, Alzheimer's will only become a greater threat, and looms large if we don't figure out how to prevent its ravages. Let's not overlook that hospitals and nursing homes don't ever go generic. Medicines do. We shouldn't be discouraging their development when the costs of leaving Alzheimer's untreated are already so high, and growing.

What we pay for branded medicines is an investment, not an expense, because they go generic and become inexpensive public goods. What we pay for branded drugs is akin to a mortgage in

that way. It's finite. What we pay for hospitals and nursing homes is an eternal and rising rent. Not paying a mortgage for a home is no way to save when you live in an apartment with rising rent.

Need to guarantee market and government discounts for beneficiaries, not health plans

There are reasons for ongoing public outrage over drug prices and why Congress felt compelled to respond to that outrage. But consider how insurers and the Pharmacy Benefit Managers (PBMs) they own or contract with are able to jack up the prices of even inexpensive generic drugs by 100-fold[4] so that they can charge patients massive out-of-pocket costs, on top of all the premiums those people have paid their whole lives. Recently, the Wall Street Journal found that health plans are marking up the cost of generic versions of the oncology drug Gleevec that costs as little as $55 for a month's supply. Instead plans are charging $6,600 per month to their premium-paying members.[5] This isn't just outrageous from a cost and government oversight perspective, it also harms patients when you consider that 50% of cancer patients abandon prescribed treatments when out-of-pocket costs exceed $2000/year (40% abandon care when OOP costs are between $500 & $2000/year)[6].

It should be clear that the prices patients have been outraged about have been the prices imposed on them by their own insurance plans, including Medicare plans. In some instances, a recent GAO report[7] found, Medicare patients were paying four times as much out-of-pocket for drugs than it cost their Medicare Part D plan for the same medicine.[8] The solution, as part of the

[4]https://www.wsj.com/health/healthcare/generic-drugs-should-be-cheap-but-insurers-are-charging-thousands-of-dollars-for-them-ef13d055

[5]https://www.wsj.com/health/healthcare/generic-drugs-should-be-cheap-but-insurers-are-charging-thousands-of-dollars-for-them-ef13d055

[6] https://www.nytimes.com/2023/02/07/health/medicine-insurance-payments.html

[7] https://www.gao.gov/products/gao-23-105270

[8]https://www.marketwatch.com/story/medicare-patients-paid-4-times-as-much-as-their-drug-plans-for-certain-medicines-study-finds-73f174ea

IRA partially acknowledges, is setting out-of-pocket caps that help ensure insurers actually pass savings on to Medicare beneficiaries and ensure Medicare price-set drugs are placed on the lowest formulary tiers.

We all pay for medicines via our premiums. They aren't supposed to come with unaffordable out-of-pocket costs when we get sick. We don't need patients to have more skin in the game than their own disease. No one fakes cancer so they can get chemo that they don't actually need. Insurance plans increasingly require that physicians seek prior authorization before agreeing to cover a medicine, ostensibly to make sure that it's right for the patient. Insurance plans already require patients to "step through" cheaper drugs that might work for them before moving on to alternatives. So why then do plans charge any out-of-pocket, whether deductible, co-pay, or co-insurance, for a medicine that the plan explicitly confirms is appropriate for a patient? That's the question we need to be asking ourselves because patients are rightfully outraged that they can't afford the medicines even their own plan agrees are right for them, after a lifetime of paying premiums. And all the rest of us are justified to be outraged right along with them, because we are all patients, now or eventually.

Medicare negotiation of small molecule drug prices after just nine years on the market does nothing to lower patients' out-of-pocket costs to make them more affordable to America's seniors. In fact, CMS annually approves Medicare Advantage plans that charge tens of millions of beneficiaries 50% coinsurance on list prices for both Part D and Part B drugs and there is nothing in CMS' recent IRA guidance that will stop those plans from doing so in the future.[9]

Furthermore, nothing in the so-called SMART Act, which proposes imposing those same price controls on all medicines just five years after they launch, lowers patient out-of-pockets. These

[9] https://www.kff.org/medicare/issue-brief/medicare-part-d-a-first-look-at-medicare-drug-plans-in-2023/ https://www.medicarerights.org/medicare-watch/2022/03/17/new-kff-report-examines-beneficiary-exposure-to-part-b-drug-costs

proposals are simply not designed to make medicines more affordable to patients. These price controls only lower what insurance itself pays for these medicines but unless there are out-of-pocket caps, insurance is still free to layer on any fees it likes, as it does with discounted brand and inexpensive generic drugs. One might argue that price controls lower what taxpayers pay for these medicines via Medicare. But by drastically reducing the incentives for investment in R&D, these price controls are only condemning all of us taxpayers to pay ever more for hospitals and nursing homes, allowing disease to impose its pain and loss on all of us while running up a massive bill.

The looming threat and cost of disease mirrors the looming threat and cost of global warming. Why then did the IRA take a hundred-year view of global warming and create massive incentives for new technologies to reduce carbon emissions and bend the long-term cost curve but take only a ten-year budgetary view of cancer and Alzheimer's to disincentive new medicines?

Most of the medicines chosen for negotiation this year will have had around 14 years of market-based pricing before the IRA reduces their prices. That's about what investors and innovators would have expected when embarking on their development. In any case, they can't be uninvented. But I'm worried about today's early-stage cancer drug development programs. If we're lucky, these are the molecules that the FDA might approve in 2030.The IRA would target any successful ones for price controls in 2039. These drugs haven't been invented yet. If the IRA's small molecule price controls kick in at nine years, they may never be.

In creating the IRA's nine-year penalty, the government has created a toxic side effect for NDA-path drug development, which includes traditional small molecules and peptides as well as newer modalities like oligonucleotides. These are cutting edge tools in the fight against the

disease. Now I can't work with them because investors today don't want to fund early-stage programs that will suffer the nine-year penalty.

There's a reason why 14 years has been the average duration of patent-protected market-pricing. It's because whenever anyone pitches a project that would have far less time on the market, investors don't fund it. We should be worried about the small molecule programs we don't see making it to market. The ones that are now unfundable.

Nine years is far shorter than 14[10], especially when you consider that between the challenges of securing reimbursement and proving that the drug works in different stages of a disease, revenues take a while to ramp up. Truncating a drug's marketability by five years can cut its profitability by half.[11] By comparison, the 13 years afforded to biologic drugs before Medicare negotiation knocks their price down is close enough to 14 not to alter how we think about their rewards. We need small molecules to get the same 13 years as biologics. That is close enough to the 14 years that has long been adequate. I hope Congress recognizes that the goal here is not just establishing parity between small and large molecules but ensuring that there are adequate incentives for development of all worthy medicines, because we have a lot of pain and cost to avert.

Science certainly wouldn't lead us to a policy that prioritizes large molecules over small molecules. In both neurodegenerative diseases (Alzheimer's, Parkinson's, etc.) and cancer brain metastases, small molecules are the weapon of choice over biologics because of their ability to penetrate the blood-brain barrier. If a biologic kills off all cancer cells in the body but cannot cross the blood-brain barrier, the cancer could come back lethally as brain metastases.

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[10] How do I get to 14? Patents last 20 years, but a lot of that patent life is eaten up by the drug development process. Up to five years of patent life can be restored via the Hatch-Waxman Act, a decades-old law designed to both incentivize drug development and create a thriving generics market. [TK insert citation to Kesselheim paper]

[11]

We need both small molecule and biologic weapons in our toolkit, and one cannot substitute for the other. It's not like small molecules cost less to develop or are less risky to develop than biologics. Their development has simply been rendered much less rewarding to investors.

A plan to mitigate IRA's negative impact on small molecule R&D

Policymaking need not be a zero sum game. We can balance biotech affordability and innovation. We can mitigate the IRA's unintended consequences. Policymakers can restore sufficient R&D incentives for new small molecules simply by having the government treat small and large molecules the same after 13 years. An increase in the minimum statutory discount can more than pay for a change that treats small and large molecules the same. For those who equate harming biotech with helping patients or say biotech must pay for any changes to the law: this compromise allows you to say "we still got them and they still will pay!"

We can make drug pricing & insurance reform work

Our system doesn't always work as it should. Sometimes reward periods last longer than intended by the patent system (and longer than the investors who funded the R&D expected or needed to justify their investment). **We should all celebrate as drugs go generic** – after they have generated a return on investment for their inventors and investors – it means we have fulfilled our mission and done our duty to society by delivering a public good that will forever leave society better off. To keep generating a return, we must then keep innovating; we must then keep addressing other unmet needs; we must develop treatments for other diseases where society would value a better treatment. That's the intent of the patent system and the result of our market system. Together, market-based pricing for a patent-defined period of time is how the market guides investment where it's needed.

We could talk about how other countries pay less, freeloading off the US just as they do when it comes to military spending and global defense. If there were a way to get other countries to pay more, it would lessen what investors have to count on the US to pay. Maybe Congress can encourage the State Department to negotiate with other countries. Any one drug company has to make the choice between those countries not paying for the drug at all or paying some lower price. Some revenue is better than no revenue. Like bad roommates, these countries enjoy the benefits of living under a roof for which the US is the primary mortgage payor. They get delayed access to new medicines like a bad roommate might settle for a cold shower or uncomfortable futon, but if the US insisted on paying as little as these other countries, the end result would be that R&D would dry up. The risks and costs of drug development are what they are and the stinginess of other countries is what it is. The question facing America is how it wants to deal with the burden of disease. Do we just accept it and face rising hospital and nursing home costs? Or do we invest, via the small portion of insurance premiums and Medicare taxes that we collectively spend on branded drugs, in incentives to address these diseases better with medicines.

We spend over $4 Trillion annually on healthcare in the US. But only 8.8% of that spending goes to branded drugs and about 2% goes to generic drugs[12]. Over 80% of that spending goes to hospitals and clinics and doctors and nursing homes. If we want to reduce what we spend on hospitals and clinics and nursing homes, on that massive 80% chunk of our premiums that goes to healthcare services, we have to prevent diseases from putting us into hospitals and landing us in nursing homes in the first place. A big part of how we do that is with new medicines. So 10% of our premiums are helping to mitigate the rise of 80% of our premiums. And yet, it's novel

[12] NHE of $4.3 trillion in 2021, and prescription drug spending of $378.0 billion in 2021 (8.8%) https://www.cms.gov/data-research/statistics-trends-and-reports/national-health-expenditure-data/nhe-fact-sheet

medicines that are being price controlled, removing a major check on the rise of healthcare services.

If one were to snap their fingers and convert all branded drugs into generics, it would reduce our premiums by about 9% by cutting branded drug spending by 90%. We would shave 9% off our premiums in an instant. In most cases, these drugs would have gone generic within 14 years regardless. And yet, by rushing to enjoy those savings, we would have eliminated the incentives for investment in new R&D that would have generated a whole new generation of medicines that could have averted the rise of healthcare services spending. Our insurance premiums would rapidly grow to eat up the branded drug savings, and then some.

Where will the money come from to support an aging population? That's a big question. But everything we enjoy comes from the productivity of a working age population. Working age used to be into one's 40s. Then 50s. And with modern medicines, people now can work into their 60s or beyond. We set retirement at around 65 and switch to Medicare at that age. But if we aspire to living longer, healthier lives, then it opens up the possibility that we might work longer to make that possible. That's our moonshot. That's our Mars mission. Cutting incentives for innovation will leave us where we are.